REMARKS

Claims 1-18, 22-25, 28-30, 32-34, 36-44, 46-56, and 59-61 are pending. Claims 4, 5, 13, 14, 18, 23, 25, 39, 40, 49, and 51-53 are cancelled without prejudice, and claims 62-100 have been added. Claims 1-3, 6-12, 15-17, 22, 24, 28-30, 32-34, 36-38, 41-44, 46-48, 50, 54-56, and 59-100 will therefore be pending upon entry of the proposed amendments.

Applicants acknowledge that claim 32 is allowed.

The Examiner has indicated that claims 6-10, 15-17, 41-43, 50-53, 56, and 61 are "objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form" (Office Action, page 13). Claims 6-10, 15-17, and 41-43 are directed to compounds of formula (I) in which the variable "Ar" is either a heterocyclic ring (e.g., claims 6-9) or R^9-phenyl (e.g., claim 10).

Applicants have amended the definition of variable "Ar" in independent claims 1 and 28 to exclude "phenyl" and "naphthyl" as permissible substituents. As such, claims 1 and 28 as currently amended are directed to compounds in which the variable "Ar" is either a heterocyclic ring or R^9-phenyl. Applicants have amended dependent claims 2 and 3 to be consistent with claim 1 as currently amended and amended dependent claim 47 to be consistent with claim 28 as currently amended.

Applicants have amended claims 36 and 37 to correct a punctuation error.

Applicants have amended the definition of the variable "Ar" in independent claim 48 to exclude "phenyl, optionally substituted with F, Cl, Br , C_{1-6} alkyl, CF_3, hydroxyl, C_{1-6} alkoxy, OCF_3, NO_2, amino, alkylamino, dialkylamino, methylcarboxyl, aminocarbonyl, or SR^7; wherein R^7 is H or C_{1-6} alkyl; 1- naphthyl, 2- naphthyl" as permissible substituents. As such, claim 48 as currently amended is directed to compounds in which the variable "Ar" is a heterocyclic ring. Applicants have amended claim 50 to be consistent with claim 48 as currently amended.

New claims 62-100 are directed to compounds in which the variable "Ar" is either phenyl or naphthyl. The specific subject matter of each of the new claims 62-100 is discussed in more detail below.

New claims 62-66 include the subject matter that was cancelled in claims 1, 2 ,3, 4, 5, respectively. New claims 67 and 68 include the subject matter of presently pending claims 11 and 12. New claims 69 and 70 include the subject matter that was cancelled in claims 13 and 14, respectively. New claim71 includes the subject matter of claim 18, now cancelled. New claims 72-75 include the subject matter of claims 22, 23 (now cancelled), 24, and 25 (now cancelled), respectively. New claim 76 includes the subject matter that was cancelled in claim 28. New claims 77, 78, 79, 80, 81, 82, and 83 include the subject matter of presently pending claims 29, 30, 33, 34, 36, 37, and 39, respectively. New claims 84 and 85 include the subject matter of cancelled claims 39 and 40, respectively. New claims 86 and 87 include the subject matter of presently pending claims 44 and 46. New claim 88 includes the subject matter that was cancelled in claim 47. New claim 89 includes the subject matter that was cancelled in claim 48. New claim 90 includes the subject matter of cancelled claim 49. New claim 91 includes the subject matter that was cancelled in claim 50. New claims 92, 93, and 94 include the subject matter of cancelled claims 51, 52, and 53, respectively. New claims 95, 96, 97, 98, 99, and 100 include the subject matter of presently pending claims 54, 55, 56, 59, 60, and 61, respectively.

No new matter is introduced by these amendments.

Rejection under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 1-5, 11-14, 18, 22-25, 28-30, 33, 34, 36-40, 44, 46-49, 54, 55, 59, and 60 as being unpatentable over Isaac, M. et al., *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1719-1721 (Isaac).

The rejection of claims 4, 5, 13, 14, 18, 23, 25, 39, 40, and 49 is moot in view of their cancellation.

As discussed elsewhere, independent claims 1 and 28 as currently amended are directed to compounds in which the variable "Ar" is either a heterocyclic ring or R^9-phenyl, and independent claim 48 as currently amended is directed to compounds in which the variable "Ar" is a heterocyclic ring. The Examiner has indicated that claims 6-10, 15-17, and 41-43, which are directed to compounds of formula (I) in which the variable "Ar" is either a heterocyclic ring (e.g., claims 6-9) or R^9-phenyl (e.g., claim 10), "would be allowable if rewritten in independent form" (Office Action, page 13). In view of the foregoing, Applicants submit that claims 1-3, 11,

12, 22, 24, 28-30, 33, 34, 36-38, 44, 46-48, 54, 55, 59, and 60 in their presently amended form are directed to allowable subject matter. Applicants respectfully request that the rejection be reconsidered and withdrawn in view of the foregoing amendments and remarks.

Applicants have also presented new claims 62-100 for consideration by the Examiner, which are directed to compounds of formula (I) in which the variable "Ar" is either phenyl or naphthyl. Applicants submit that claims 62-100 are patentable over Isaac on the grounds that the compounds covered by claims 62-100 possess a property --the ability to reduce food intake-- that is **not** possessed by the compounds disclosed in Isaac. This is discussed in more detail below and in the accompanying declaration made by inventor Patrizia Caldirola under 37 C.F.R. § 1.132 ("the declaration").

In order for a *prima facie* case of obviousness of a chemical composition to be established there must be "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions." *In re Dillon* 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (*In Banc*). The Federal Circuit in *Dillon* also held that the *prima facie* case can be rebutted with a showing that "**the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have**" (*Id.* at 1901, emphasis added).

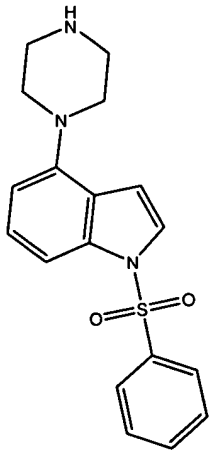
The aforementioned declaration describes experimental data concerning:

(1) the effect of 1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole (disclosed as Example 7 in USSN 10/037,110 at page 23, lines 7-15 of the Specification; referred to as "Applicants' Example 7 compound") and 1-[(2,5-dimethoxyphenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole (disclosed as Example 8 in USSN 10/037,110 at page 23, lines 17-26 of the Specification; referred to as "Applicants' Example 8 compound") on food intake in ob/ob mice; and

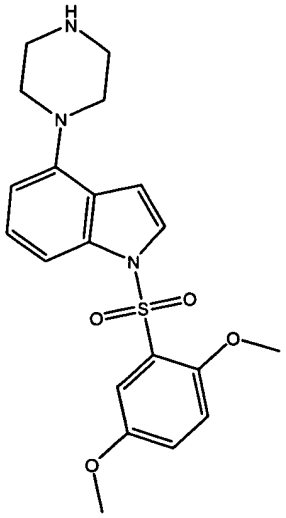
(2) the effect of the 5-HT6 antagonist "compound **4a**," which is disclosed in Isaac, M. et al., *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1719-1721 (Isaac) on food intake in ob/ob mice.

The structures of the compounds disclosed in Examples 7 and 8 and compound **4a** are shown in Chart I.

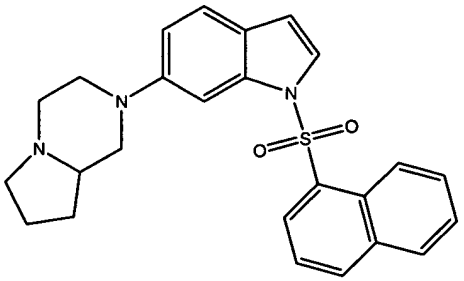
Chart I



Example 7



Example 8



Compound 4a

The indole ring in each of Examples 7 and 8 is substituted at the 4-position with a piperazinyl ring, while the indole ring in compound **4a** is substituted at the 6-position with a bicyclopiperazinyl ring.

As explained in greater detail below, Applicants' Example 7 compound reduced food intake in obese ob/ob mice at dosages of 3 mg/kg/day, 10 mg/kg/day, 30 mg/kg/day, 50 mg/kg/day and 130 mg/kg/day (% of basel level = 63%, 53%, 33%, 25%, and 16%, respectively); Applicants' Example 8 compound also reduced food intake in obese ob/ob mice at dosages of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (% of basel level = 62.8%, 53.4%, 32.8%, respectively); and compound **4a** did not reduce food intake at any of the tested dosages (10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day). This is particularly striking given that compound **4a** had a K_i for 5-HT_6 that was the lowest of all compounds tested in Isaac. Thus, a person of ordinary skill in the art would conclude that compound **4a** was the most potent 5-HT6 inhibitor.

The experiments conducted to evaluate the effect of Applicants' Example 7 compound, Applicants' Example 8 compound, and compound **4a** are discussed in more detail below.

Experimental Protocol

Applicants' Example 7

I. Obese ob/ob mice were divided into four groups, referred to as "Groups 7-A, 7-B, 7-C, and 7-D." Each of the aforementioned groups contained 8 mice.

Group 7-A was treated with vehicle only (saline) on the day of treatment and thus served as a control group. Groups 7-B and 7-C were each treated with different dosages of Applicants' Example 7 compound on the day of treatment: each of the 8 mice in Group 7-B was dosed at 50 mg/Kg/day, and each of the 8 mice in Group 7-C was dosed at 150 mg/Kg/day. Finally, Group 7-D was treated with *m*-chlorophenylpiperazine (*m*CPP, a known 5-HT_{2c} agonist) on the day of treatment and thus served as a positive control group.

II. Obese ob/ob mice were divided into five groups, referred to as "Groups 7-A', 7-B', 7-C', 7-D', and 7E'." Each of the aforementioned groups contained 8 mice.

Group 7-A' was treated with vehicle only (saline) on the day of treatment and thus served as a control group. Groups 7-B', 7-C', 7-D', and 7E' were each treated with different dosages of Applicants' Example 7 compound on the day of treatment: each of the 8 mice in Group 7-B' was dosed at 3 mg/Kg/day; each of the 8 mice in Group 7-C' was dosed at 10 mg/Kg/day; each of the 8 mice in Group 7-D' was dosed at 30 mg/Kg/day; and each of the 8 mice in Group 7-E' was dosed at 50 mg/Kg/day.

Applicants' Example 8

Obese ob/ob mice were divided into five groups, referred to as "Groups 8-A, 8-B, 8-C, 8-D, 8-E." Each of the aforementioned groups contained 8 mice.

Groups 8-A was treated with vehicle only (saline) on the day of treatment and thus served as a control group. Each of the 8 mice in Group 8-B was dosed with 3 mg/Kg/day of Applicants' Example 8 compound; each of the 8 mice in Group 8-C was dosed with 10 mg/Kg/day of Applicants' Example 8 compound, and each of the 8 mice in Group 8-D was dosed with 30 mg/Kg/day of Applicants' Example 8 compound. Finally, Group 8-E was treated with (*m*CPP) on the day of treatment and thus served as a positive control group.

*Isaac's Compound **4a***

Obese ob/ob mice were divided into five groups, referred to as "Groups **4a**-A, **4a**-B, **4a**-C, **4a**-D, **4a**-E." Again, each of the aforementioned groups contained 8 mice.

Group **4a**-A was each treated with vehicle only (saline) on the day of treatment and thus served as a control group. Each of the 8 mice in Groups **4a**-B was dosed with 10 mg/Kg/day of Isaac's Compound **4a**; each of the 8 mice in Groups **4a**-B was dosed with 30 mg/Kg/day of Isaac's Compound **4a**; and each of the 8 mice in Groups **4a**-B was dosed with 100 mg/Kg/day of Isaac's Compound **4a**. Finally, Group **4a**-E was treated with (*m*CPP) on the day of treatment and thus served as a positive control group.

Food Intake Data

"Mean Pre-treatment (g/15h)" for a particular group refers to the mean weight (g = grams) of food consumed per mouse over a 15 hour period on the day before treatment (**basal**). "Mean Post-treatment (g/15h)" for a particular group refers to the mean weight (grams) of food consumed per mouse over a 15 hour period after treatment with the test compound. The term "% of basal level" refers to quotient of:

Mean Post-treatment (g/15h)/Mean Pre-treatment (g/15h)

For example, if a particular group consumed on average 6.0 g of food per animal over a 15 hour period on the day before treatment (basal) and then consumed only 1.5 g of food over a 15 hour period after treatment with the test compound, then the "% of basal level" for that particular group would be 25% (i.e., the animal's food consumption after treatment was only 25% of that observed on the day before treatment). A "% of basal level" of less than 100% means that post-treatment food consumption was lower than pre-treatment food consumption. As such, the lower the "% of basal level" (both in absolute value and relative to the % of basal level of a control (i.e., untreated) group), the more effective the test compound is at reducing food intake.

Food Intake Data for Applicants' Example 7 Compound

I. As explained in paragraph 5 of the declaration, the greatest reduction in food intake was observed in Group 7-C (% of basal level = 16%), in which Applicants' Example 7 compound was administered at a dosage of 130 mg/kg/day. The % of basal level for Group 7-C (16%) was significantly lower than that observed for the control group 7-A (77%). In fact, the % of basal level for Group 7-C was the lowest observed in any of the experiments described herein.

Reduction in food intake was also observed in Group 7-B (% of basal level = 39%), in which Applicants' Example 7 compound was administered at a dosage of 50 mg/kg/day. The % of basal level for Group 7-B (39%) was lower than that observed for the control group (77%) and was comparable to that observed in the positive control group 7-D (45.9%) in which *m*CPP was administered at a dosage of 30 mg/kg/day.

II. As explained in paragraph 5 of the declaration, the greatest reduction in food intake was observed in Group 7-E' (% of basal level = 25%), in which Applicants' Example 7 compound was administered at a dosage of 50 mg/kg/day. The % of basal level for Group 7-E' (25%) was significantly lower than that observed for the control group 7-A (73%).

Reduction in food intake was also observed in Group 7-D' (% of basal level = 33%), in which Applicants' Example 7 compound was administered at a dosage of 30 mg/kg/day. The % of basal level for Group 7-D' (33%) was significantly lower than that observed for the control group (73%).

Reduction in food intake was also observed in Group 7-C' (% of basal level = 53%), in which Applicants' Example 7 compound was administered at a dosage of 10 mg/kg/day. The % of basal level for Group 7-C' (53%) was lower than that observed for the control group (73%).

Finally, statistically meaningful reduction in food intake was even observed at relatively low dosages (3 mg/kg/day) of Applicants' Example 7 compound (see data for Group 7-B').

Food Intake Data for Applicants' Example 8 Compound

As explained in paragraph 6 of the declaration, the greatest reduction in food intake was observed in Group 8-D (% of basal level = 32.8%), in which Applicants' Example 8 compound

was administered at a dosage of 30 mg/kg/day. The % of basal level for Group 8-D (32.8%) was significantly lower than that observed for the control group 8-A (68.0%).

Reduction in food intake was also observed in Group 8-C (% of basal level = 53.4%), in which Applicants' Example 8 compound was administered at a dosage of 10 mg/kg/day. The % of basal level for Group 8-C (53.4%) was lower than that observed for the control group and was comparable to that observed in the positive control group 8-E (45.9%) in which *m*CPP was also administered at a dosage of 10 mg/kg/day.

Finally, a statistically meaningful reduction in food intake was even observed at relatively low dosages (3 mg/kg/day) of Applicants' Example 8 (see data for Group 8-B).

Food Intake Data for Compound 4a and Comparison with Food Intake Data for Applicants' Example 7 and Applicants' Example 8

As explained in paragraph 7 of the declaration, compound **4a** was not effective in reducing food intake in the obese ob/ob mouse model.

The % of basal level for Group **4a**-B (79.55%) was actually slightly higher than the % of basal level for the control group **4a**-A (75.21%). This means that there was effectively no reduction in food intake when the animals were dosed with 10 mg/kg/day of Isaac's compound **4a**.

In contrast, when the animals were dosed with 10 mg/kg/day of Applicants' Example 7 compound (see data and discussion for Group 7-C'), the % of basal level for Group 7-C' (53%) was lower than that observed for the control group (73%). Thus, food intake was lowered in Group 7-C' (10 mg/kg/day of Applicants' Example 7 compound), but not in Group **4a**-B (10 mg/kg/day of Isaac's compound **4a**).

Again, in contrast with Isaac's compound **4a**, when the animals were dosed with 10 mg/kg/day of Applicants' Example 8 compound (see data and discussion for Group 8-C), the % of basal level for Group 8-C (53.4%) was lower than that observed for the control group (68.0%) and was comparable to that observed in the positive control group 8-E (45.9%). Thus, food intake was lowered in Group 8-C (10 mg/kg/day of Applicants' Example 8 compound), but not in Group **4a**-B (10 mg/kg/day of Isaac's compound **4a**).

The % of basal level for Group **4a**-C was essentially the same as the % of basal level for the control group **4a**-A. This means that there was effectively no reduction in food intake when the animals were dosed with 30 mg/kg/day of Isaac's compound **4a**.

In contrast, when the animals were dosed with 30 mg/kg/day of Applicants' Example 7 compound (see data and discussion for Group 7-D'), the % of basal level for Group 7-D' (33%) was lower than that observed for the control group (73%). Thus, food intake was lowered in Group 7-D' (30 mg/kg/day of Applicants' Example 7 compound), but not in Group **4a**-C (30 mg/kg/day of Isaac's compound **4a**).

Again, in contrast with Isaac's compound **4a**, when the animals were dosed with 30 mg/kg/day of Applicants' Example 8 compound (see data and discussion for Group 8-D), the % of basal level for Group 8-D (32.8%) was lower than that observed for the control group (68.0%). Thus, food intake was lowered in Group 8-D (30 mg/kg/day of Applicants' Example 8), but not in Group **4a**-C (30 mg/kg/day of Isaac's compound **4a**).

Finally, even at a relatively high doses, Isaac's compound **4a** was not effective at reducing food intake (see data for Group 4a-D, in which the animals were dosed with 100 mg/kg/day of Isaac's compound **4a**).

In contrast, when the animals received a relatively high dose of Applicants' Example 7 compound (see data and discussion for Group 7-C in the declaration), the % of basal level for Group 7-C (16%) was significantly lower than that observed for the control group 7-A (77%) and was the lowest value observed in any of the experiments described herein. Thus, food intake was lowered in Group 7-C (dosed with 130 mg/kg/day of Applicants' Example 7), but not in Group **4a**-D (dosed with 100 mg/kg/day of Isaac's compound **4a**), even with the use of a relatively high dose of Isaac's compound **4a**.

Conclusion

Isaac's compound **4a**, although a 5-HT_6 antagonist (as well as the most potent 5-HT_6 antagonist disclosed in Isaac), was not effective at reducing food intake in the obese ob/ob mouse model at any of the tested dosages. By comparison and in contrast, Applicants' Example 7 and Example 8 were shown to be effective at reducing food intake in the obese ob/ob mouse model, and were effective in doing so over a relatively wide range of dosages. Thus, on the basis of the

foregoing animal model, Applicants' Example 7 compound and Example 8 compound possess the ability to reduce food intake, while Isaac's compound **4a** does not.

Applicants submit that the compounds covered by claims 62-100 are not *prima facie* obvious over Isaac because the claimed compounds possess a property that the Isaac compounds do not have, namely the ability to reduce food intake. Applicants respectfully request that the rejection not be applied to new claims 62-100.

CONCLUSION

Enclosed is a $1,020 check for the Three Month Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No.: 13425-052001.

Respectfully submitted,

Date: November 23, 2005

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